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Multivariate surface-based analysis of corpus callosum in patients with sickle cell disease

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Abstract

Sickle cell disease (SCD) is a genetic hematological disease in which the hemoglobin molecule in red blood cells is abnormal. It is closely associated with many symptoms, including pain, anemia, chest syndrome and neurocognitive impairment. One of the most debilitating symptoms is elevated risk for cerebro-vascular accidents. The corpus callosum (CC), as the largest and most prominent white matter (WM) structure in the brain, can reflect the chronic cerebrovascular damage resulting from silent strokes or infarctions in asymptomatic SCD patients. While a lot of studies have reported WM alterations in this cohort, little is known about the shape deformation of the CC. Here we perform the first surface morphometry analysis of the CC in SCD patients using four different shape metrics on T1-weighted magnetic resonance images. We detect regional surface morphological differences in the CC between 11 patients and 10 healthy control subjects. Differences are located in the genu, posterior midbody and splenium, potentially casting light on the anatomical substrates underlying neuropsychological test differences between the SCD and control groups.

Keywords

sickle cell disease; corpus callosum; multivariate tensor based morphometry

1. INTRODUCTION

Sickle cell disease (SCD) is defined as a group of autosomal recessive hemoglobinopathies in which the hemoglobin molecule in red blood cells is abnormal. The abnormal hemoglobin

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can cause red blood cells to become sickle-shaped and rigid, tending to occlude blood vessels and capillaries. SCD is closely associated with many symptoms, including pain, anemia, chest syndrome, and neurocognitive impairment^{1–2}. Of all the symptoms, cerebral-vascular complications, such as intracranial hemorrhage, strokes and infarctions, are the most concerns of physicians, knowing that the stroke incidence and re-occurrence rate in SCD group is much greater³.

Previous brain imaging studies in SCD have revealed delayed brain development, and grey matter (GM) and white matter (WM) loss compared with healthy control subjects^{4–6}. These losses may be associated with behavioral and cognitive consequences. For example, previous studies reported that findings from imaging studies are associating with changes in neurocognitive impairments, such as lower verbal intelligence quotient scores, poorer math performance, and visuo-motor impairments in children with SCD^{5,7–8}.

The corpus callosum consists of 200–250 million axonal projections and is the largest and most prominent (WM) structure in the brain, connecting the two hemispheres. Given the chronic cerebral-vascular microscopic damage and vulnerability to strokes in SCD patients, the CC is of particular interest due to its midline location and complex neuronal pathways. Regional CC damage in SCD patients has been shown in imaging studies and is associated with subtle decrease in neurocognitive test scores^{7,9}. These structural changes in the CC can reflect the deep WM alterations resulting from silent stroke or infarction in asymptomatic SCD patients, and point to potential underlying anatomical correlates of neuropsychological test discrepancies between the SCD and control groups.

While a lot of studies have reported WM tract impairment and volume decrease in this cohort, little is known about surface deformation in the corpus callosum (CC), and its relationship to neuropsychological scores^{9–10}. Past morphometry-based studies involved either whole CC volume analysis, or whole brain voxel-wise analysis that did not zoom in specifically on the CC^{11–12}. Shape analysis is complementary to these other methods, and may help localize chronic alterations on the surface of the CC. In this paper, we performed statistical surface comparisons between a SCD and a control group using four surface multivariate tensor-based morphometry statistics¹³, which are combinations of the thickness and directional surface area differences between structures.

2. METHOD

2.1 Dataset and Preprocessing

The study was approved by the Institutional Review Board at Children's Hospital Los Angeles. All patients were recruited with consent or assent. Our dataset consists of neurophysiological test outcomes and brain MRI images, including T1-weighted images, T2-weighted images and magnetic resonance angiography (MRA). T2-weighted images were acquired and read to find WM abnormalities by a licensed neuro-radiologist blinded to disease status during the study. MRA images were used to identify patients with artery stenosis. T1-weighted images were collected for co-registration, segmentation and morphometry purposes.

After excluding 2 patients with overt stroke and one subject with severe, bilateral proximal anterior cerebral artery stenosis, our final dataset contains 11 clinically asymptomatic SCD patients' brain MRIs (age=24.7±11.2; F=6, M=5) that were compared against 10 age and gender matched healthy controls (age=19.3±3.1; F=7, M=3). Other exclusion criteria included acute chest syndrome, pregnancy, and pain crisis hospitalization within one month of the study. All subjects recruited were either African American or Hispanic.

Exams were obtained for 21 subjects on a 3T-Phillips Achieva. Table 1 shows our imaging parameters of T1 images. Neurophysiological tests were done within one week of the imaging studies. Full-scaled intelligence quotient (FSIQ), verbal and symbolic memory and executive function scores were collected and standardized to the same scale.

2.2 Registrations and 3D Segmentation

We performed bias field correction and removed all non-brain parts on 3D T1 images using Brainsuite¹⁴. Images were then registered to the T1 standard Montreal Neurological Institute (MNI) ¹⁵ space using the FLIRT¹⁶ linear registration algorithm.

After registration, we manually segmented CCs from the whole brain T1 images for each individual with Insight Toolkit's SNAP program¹⁷. Tracings were performed in the MNI space using standard protocols. We consulted a board-certified neuro-radiologist to help guide the placement of the contours. Our inter-rater average percent volume overlap (intersection of volumes over average of them) for segmenting twice at a month's interval is above 94%.

2.3 Surface-based Morphometry analysis

To investigate the regional alterations in the CC, we performed a multivariate surface tensor based morphometry analysis (MTBM)^{18,19}. Based on the binary segmentation described above, 3D representations of the CCs were constructed using a marching cube algorithm²⁰. Subsequently, surface models were parameterized by conformally mapping to a rectangle. This was followed by a constrained harmonic registration between each individual CC model and an intermediate surface²¹, where vertex-wise correspondence was obtained. On each vertex of the CC surface, group analyses were carried out as follows:

1. Univariate student t-tests were performed on the medial distance (MAD), representing the thickness of the corresponding location¹⁸.
2. Univariate student t-tests were performed on the determinant of the Jacobian matrix (*detJ*) from the registration to the reference surface, representing changes in surface area between the reference and each subject's images.
3. Multivariate Hotelling T² tests were performed on the logged deformation tensors ($\log JJ^T$), providing directional differences in area, and thus a more complete descriptor of the deformation in the registration than the univariate *detJ*²².
4. Multivariate Hotelling T² tests were performed on the combined medial distance and logged deformation tensor (MADMTBM), which have shown to increase detection power, according to our previous neonatal and adult studies^{18,23–24}.

3. RESULTS

Fig. 1–4 show color-coded p-value maps for group analyses using the four different measures. The four statistics detect similar regions of alterations, with the MADMTBM method showing the highest detection power. Of the four measures, MAD shows relatively fewer clusters of significance, which are primarily located in the anterior and posterior ends of CC. *detJ* shows additional clusters in the midbody, and the two multivariate statistics (MTBM and MADMTBM) detect more widespread clusters in the genu, left side of the midbody and the splenium. After controlling for multiple comparison errors, the univariate statistics (MAD and *detJ*) fail to reach global significance ($p < 0.05$); the multivariate analysis on the logged deformation tensors shows trends of differences ($P = 0.061$); the multivariate MADMTBM analysis successfully detects significant alterations ($p = 0.0239$) between the SCD and the control groups.

4. DISCUSSION

Being the largest WM structure in the brain, the CC often exhibits anatomical alterations in response to disease. Out of the four measures, the two multivariate statistics (MTBM and MADMTBM) detected more widespread clusters in the genu, left side of the midbody and the splenium. These regions of alternations are consistent with the previous findings on the same cohort⁹ and potentially more sensitive with the controlling of multiple comparison errors. In the mean time, we found subtle decrease in neurocognitive test scores.

Various neuropsychological evaluations have been conducted on the same patients in the study. We found subtle decrease in test scores that may be related to the CC imaging changes, and will plan on correlating both types of results in the near future, as in other imaging studies of the CC^{7,9,11–12}. This will allow us to determine how these WM alterations are related to neurological impairment, and hence inform treatment. Our own results with the Delis–Kaplan Executive Function System (D-KEFS) evaluations, suggest deficiencies in executive functions of the SCD group. Furthermore, results of the California Verbal Learning Test (CVLT) indicate that the SCD group showed deficiencies in the processing of verbal memory. These group differences are consistent with prior research on SCD subjects without overt strokes and severe stenosis^{9,28}.

In the future, we would like to incorporate both T1 and DTI data into our analysis of CC, to further analyze the underlying anatomical changes associated with SCD. Due to its capacity of probing WM microstructures, DTI has been promising in detecting CC diffuse injuries, and our in-house fused T1/DTI algorithm has shown increased detection power in studies of traumatic brain injury²⁹ and aging³⁰.

This study is part of an ongoing grant and we are currently in the process of acquiring more data, which we will use to validate the observed CC alterations and extend this investigation on a larger data set.

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Figure 1. Right, left, superior and inferior view of CC using MAD. Corrected global p-value after 10,000 permutations is 0.1645.

Figure 2.

Right, left, superior and inferior view of CC using determinant of $\det J$. Corrected global p value after 10,000 permutations is 0.1893.

Figure 3. Right, left, superior and inferior view of CC using mTBM. Corrected global p-value after 10,000 permutations is 0.0610.

Figure 4. Right, left, superior and inferior view of CC using MADMTBM. Corrected global p-value after 10,000 permutations is 0.0239.

Table 1

Acquisition parameter for T1 scans.

TR	7600 msec
TE	86 msec
FOV	$240 \times 240 \times 128$ mm
Size.	$1 \times 1 \times 1$ mm